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(54) Title: PROCESS FOR PREPARING LEVOBUPIVACAINE AND ANALOGUES THEREOF**(57) Abstract**

A process for preparing levobupivacaine, racemic bupivacaine or another N-alkyl analogue thereof, comprises chlorinating pipecolic acid hydrochloride, amidation of the resultant pipecolyl chloride hydrochloride in solvent, without isolation, with 2,6-dimethylaniline, and alkylation of the resultant pipecolic acid 2,6-xylylide. Alternatively, the alkylation may be followed by the amidation.

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PROCESS FOR PREPARING LEVOBUPIVACAINE AND
ANALOGUES THEREOF

Field of the Invention

This invention relates to a novel process for the
5 manufacture of racemic bupivacaine or levobupivacaine, and
analogues thereof, from pipecolic acid.

Background to the Invention

Bupivacaine (formula I in Scheme 1) and ropivacaine
are well-known local anaesthetics. They are described in
10 US-A-4695576, GB-A-1166802, and PCT/NO83/00029. The
corresponding N-methyl and N-cyclopropyl compounds also
have such activity. However, the production of such
material on a large scale, from pipecolic acid, suffers
from various difficulties.

15 Phosphorus pentachloride has been used as a
chlorinating agent. On a large scale, its use is
problematic, in that PCl_5 is liable to react with
atmospheric moisture, and to generate waste whose
separation from the acid chloride intermediate (II) is
20 difficult. Furthermore, the phosphate waste streams which
are generated are difficult to treat or otherwise discard.

The use of acetyl chloride as the process solvent for
the production of the acid chloride (II) poses similar
difficulties.

25 Whereas isolation of the intermediate acid chloride
(II) as described in the art can be carried out on a
laboratory scale, its isolation on the larger scale is
impractical. This is due to the fact that the intermediate
(II) is a very labile substance and may decompose upon
30 exposure to atmospheric moisture.

Washing of the isolated acid chloride (II) with
commercial grade acetone, as described in the art, will
lead to its decomposition, as commercial acetone usually
contains some water.

35 Reaction of the acid chloride (II) with 2,6-
dimethylaniline in a mixture of acetone and N-
methylpyrrolidone (NMP), as advocated in the art, leads to

the formation of pipecolic acid 2,6-xylylidide (III) which is difficult to isolate from the reaction medium.

Alkylation of the intermediate (III) with 1-bromobutane and potassium carbonate in n-butanol affords
5 comparatively poor yield of the desired bupivacaine, since the reaction proceeds very slowly and usually does not go to completion.

Summary of the Invention

The present invention describes a practical and
10 streamlined one-pot process which is both economical and viable for scale-up. Furthermore, this invention may be used to manufacture racemic bupivacaine, levobupivacaine, or any corresponding N-alkylated material such as ropivacaine (Pr rather than Bu) in racemic or enantiomeric
15 form.

According to this invention, pipecolic acid is initially reacted with hydrogen chloride in a suitable solvent, furnishing pipecolic acid hydrochloride salt.

This compound is not isolated from the reaction medium
20 but is directly treated with thionyl chloride, whereupon pipecolic acid chloride hydrochloride (II) is produced. Other chlorinating agents may be used, provided that they do not contain phosphorus, e.g. oxalyl chloride.

Again, this intermediate is not isolated and is
25 conveniently treated with (2 equivalents of) 2,6-dimethylaniline. This operation generates the HCl salt of the intermediate (III) which is later isolated, after work-up. By controlling the pH, the free base can be obtained, essentially uncontaminated with 2,6-dimethylaniline (which
30 is released as the pH is increased).

Alkylation of the free base of intermediate (III) is carried out with an alkylating agent such as 1-bromobutane in a suitable solvent such as acetonitrile (ACN) or advantageously in dimethylformamide (DMF) in the presence
35 of a suitable base such as potassium carbonate. The reaction proceeds rapidly, and the resulting free base of, say, bupivacaine is isolated after removal of the solvent.

The free base may then be dissolved in a suitable solvent such as isopropanol and treated with hydrogen chloride, affording the HCl salt of, say, bupivacaine which is recovered by filtration (see Scheme 1).

5 It appears that no significant racemisation occurs during this novel process. Therefore, for example, by using enantiomerically pure (S)-pipecolic acid in this process, levobupivacaine can be produced.

Description of the Invention

10 The process of the invention is carried out by the steps described above. If desired, alkylation may precede amidation. An alternative preparation of the free base (III) is described in our International Patent Application No. PCT/GB95/02385.

15 The following Examples illustrate the invention.

Example 1 Pipecolic acid 2,6-xylylidide

Pipecolic acid (130 g) was suspended in 2 l toluene and was stirred at ambient temperature. Hydrogen chloride (40 g) was added slowly during 30 minutes.

20 The mixture was heated to 55°C and 1 g of DMF was added, followed by the addition of thionyl chloride (120 g) during 1.5 hours. The stirring at this temperature was continued until evolution of gases ceased.

25 2,6-Dimethylaniline (242 g) in toluene (250 ml) was added to the mixture at such a rate that the temperature of the mixture was maintained below 60 °C. After 2 hours, the mixture was filtered and washed with toluene (200 ml). The resulting solid was dissolved in water (2.5 l) and was treated with aqueous NaOH until its pH was raised to 4.5-
30 5.5. The liberated 2,6-dimethylaniline was removed by extraction with toluene.

The pH of the aqueous layer was raised still further, to 11-12, whereupon pipecolic acid-2,6-xylylidide (III) was liberated. This intermediate was extracted with toluene
35 and was obtained after removal of the solvent as a crystalline solid (151 g, 65% of theory).

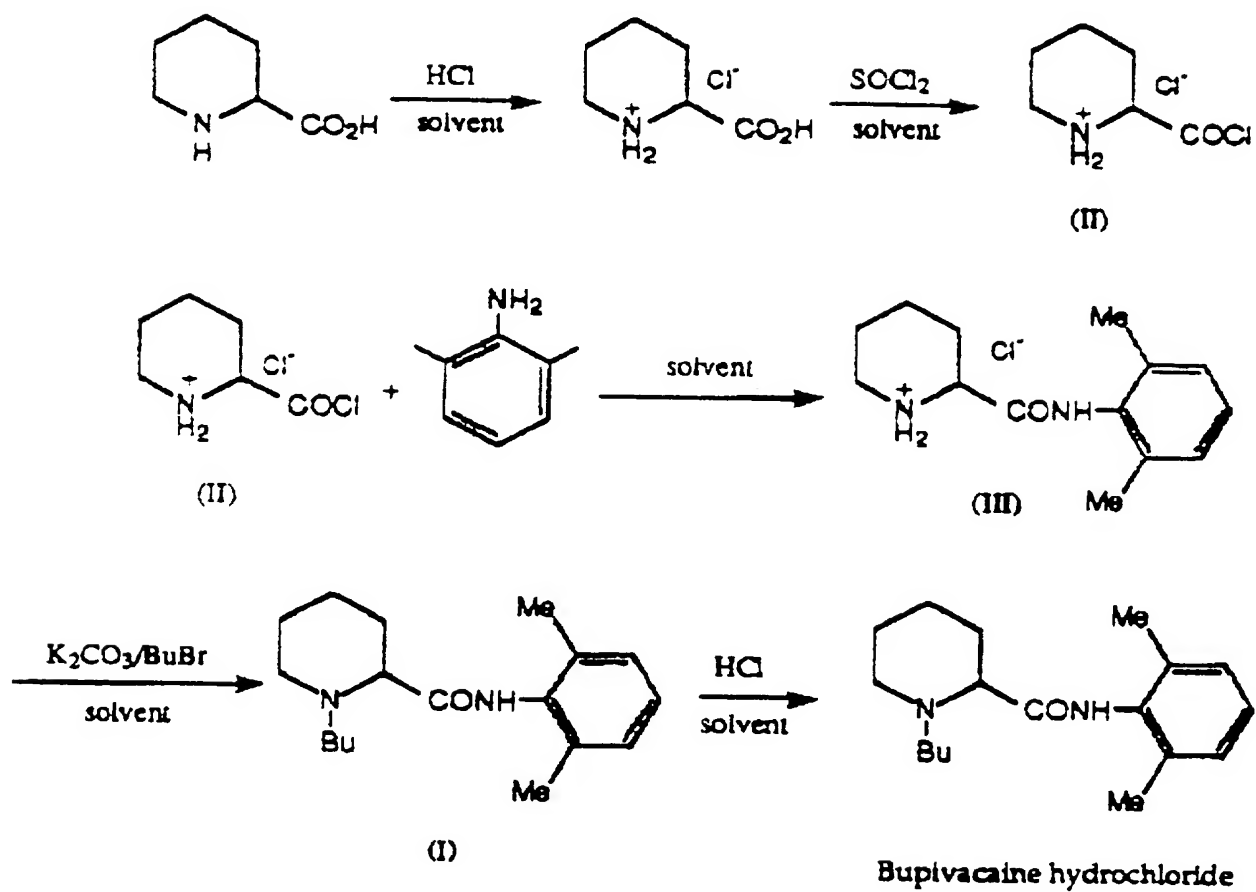
Example 2 N-n-Butylpipecolic acid 2,6-xylylidide

1-Bromobutane (90 g) was added to a suspension of
pipecolic acid-2,6-xylylidide (140 g) and a potassium
carbonate (100 g) in DMF (330 ml). The mixture was stirred
and heated at 80°C for 90 minutes and then was allowed to
5 cool to 35°C. The solids were filtered off and the DMF
solution was added to cold water (1.5 l) whereupon N-n-
butylpipecolic acid 2,6-xylylidide precipitated as a pale
cream solid (159 g, 92% theory).

Example 3 N-n-Butylpipecolic acid 2,6-xylylidide HCl salt

10 Hydrogen chloride (25 g) was introduced slowly into a
stirred solution of N-n-butylpipecolic acid 2,6-xylylidide
(145 g) in isopropanol (250 ml) at ambient temperature.
The resulting white product was filtered off, washed with
isopropanol and dried under vacuum to constant weight (161
15 g, 99% theory).

In order to prepare levobupivacaine, by the process of
the present invention, a first route involves preparing and
then resolving racemic bupivacaine. A racemisation process
is described in International Patent Application No.
20 PCT/GB95/02247. A second route involves starting from the
appropriate pipecolate enantiomer.



Scheme 1: A Novel Method for the Manufacture of Bupivacaine

CLAIMS

1. A process for preparing bupivacaine or another N-alkyl analogue thereof, which comprises the following steps:
reaction of pipecolic acid hydrochloride with a P-free
5 chlorinating agent in a solvent;
either amidation of the resultant pipecolyl chloride hydrochloride in solvent, without isolation, with 2,6-dimethylaniline, and alkylation of the resultant pipecolic acid 2,6-xylylidide; or the alkylation followed by the
10 amidation;
if desired, conversion of the resultant bupivacaine or analogue, as the free base, to a salt thereof; and
isolating the product from the reaction mixture.
2. A process according to claim 1, wherein the solvent
15 for said chloride hydrochloride is an inert solvent having a boiling point that enables the removal of excess chlorinating agent optionally together with HCl, by distillation.
3. A process according to claim 2, wherein said inert
20 solvent is a hydrocarbon, halogenated hydrocarbon or ether, more specifically toluene, methyl tert-butyl ether, tetrahydrofuran, DMF or acetonitrile.
4. A process according to any preceding claim, wherein the solvent for the alkylation solvates K_2CO_3 and is water-
25 miscible.
5. A process according to claim 4, wherein said water-miscible solvent is DMF.
6. A process according to any preceding claim, whereby (S)-pipecolic acid is converted to levobupivacaine.
- 30 7. A process according to any of claims 1 to 5, wherein the product is racemic bupivacaine.
8. A process according to any of claims 1 to 5, wherein the product is 1-propyl-N-(2,6-dimethylphenyl)-2-piperidine-carboxamide, in racemic or optically-enriched
35 form.
9. A process according to any preceding claim, wherein the amidation precedes the alkylation.

10. A process according to any preceding claim, wherein the chlorinating agent is SOCl_2 .

11. A process according to any preceding claim, wherein, following amidation, the product is separated from 2,6-
5 dimethylaniline by raising the pH.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 95/02514

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category: Citation of document, with indication, where appropriate, of the relevant passages

Relevant to claim No.

A	WO,A,85 00599 (APOTHEKERNES LAB. FOR SPECIALPRAEPARATER) 14 February 1985 cited in the application see the whole document ---	1-11
A	US,A,4 695 576 (ASTRA) 22 September 1987 cited in the application see example 2 ---	1-11
A	J. MED. CHEM., vol. 34, no. 1, 1991 pages 397-403, V. VECCHIETTI ET. AL. '(2S)-1-(Arylacetyl)-2-(aminomethyl)piperi dine Derivatives: Novel, Highly Selective k Opioid Analgesics' scheme 1 see page 398 ---	1-11

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Continuation: DOCUMENTS CONSIDERED TO BE RELEVANT

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Relevant to claim No.

A	<p>S.S. PIZEY 'Synthetic Reagents, Vol I, Chapter 4', JOHN WILEY AND SONS INC., NEW YORK, LONDON, SYDNEY, TORONTO see page 333 - page 336 -----</p>	1-11
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02514

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		AU-B- 1779683	04-03-85
		EP-A,B 0151110	14-08-85
		JP-T- 60502054	28-11-85

US-A-4695576	22-09-87	NONE	
